IN THE DRAWINGS

The attached sheets of drawings (Sheet 1 of 9 and Sheet 2 of 9) include changes to Table 1. These sheets, which include Table 1, replace the original sheets including Table 1. A footnote was added to each sheet indicating that "Eudragit NE30D" is a trademark, whose chemical name is poly(ethylacrylate, methylmethacrylate) and which has a molecular weight of 800,000.

Attachments: Replacement Sheets

REMARKS/ARGUMENTS

Claim 1 has been amended, claims 4 and 8 have been canceled, and claims 5 and 7 are pending. The specification has been amended to provide the chemical names of certain trademarked chemicals, *i.e.* Eudragit. No new matter has been added by way of this amendment.

Amendments to the Specification

The trademark Eudragit RS30D appears in the Specification at page 10, line 15. The trademarks Eudragit RS100 and RS100L appear in the Specification at page 11, line 21. The trademark EudragitNE30D appears in the Specification at Table 1. In each instance, the Specification has been amended to include the chemical names of each of these Eudragit polymers. Applicants also attach a brochure from Evonik Industries ("Exhibit A") evidencing the chemical names for each of these polymers.

Claim Amendments

Support for the limitation "poly(ethylacrylate, methylmethacrylate), and poly(ethylacrylate, methylmethacrylate)trimethyl-ammonio-ethylmethacrylate chloride" can be found in the specification in the Examples and Tables where references to Eudragit polymers is made. *See*, for example, Table 1, and the Specification at pages 10 and 11.

Support for the limitation directed to the composition of the second skin layer can be found at page 4, line 29 to page 5, line 10.

Support for the limitation of a pH-independent release can be found in claim 8.

Rejection Under 35 U.S.C. Section 112, 1st Paragraph

The Examiner has rejected claims 1, 4, 5, 7, and 8 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time of filing, had possession of the claimed invention. Specifically, the Examiner contends that the "water-insoluble acrylic polymer derivatives did not meet the written description provision…due to lacking chemical structure." (Office Action, page 2.) In view of the amendment to claim 1 to include specific acrylate polymers, this rejection is moot. Accordingly, this rejection should be withdrawn.

Rejection Under 35 U.S.C. Section 112, 2nd Paragraph

The Examiner has rejected claims 1, 4, 5, 7, and 8 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner contended that the term "softening point" was ambiguous. (*Id.* at 3.) In view of the amendment to claim 1 to include specific components of the second skin layer, this rejection is moot. Accordingly, this rejection should be withdrawn.

Rejections Under 35 U.S.C. Section 103(a)

The Examiner has rejected claims 1, 4, 5, 7, and 8 under 35 U.S.C. § 103(a) as being unpatentable over *Hara* (JP02225416) in view of *Samejima* (U.S. Patent No. 5,068,112) and *Gowan* (U.S. Patent No. 5,405,617). (*Id.* at 5.) The Examiner has also rejected the claims over *Hara* in view of *Liversidge* (U.S. Patent No. 5,145,684) and *Kokubo* (JP01287021). (*Id.* at 8.) Applicants respectfully traverse each of these rejections and submit that

even if the teachings of the collective references were combined in the manner suggested by the Examiner, the combinations would still not result in the claimed invention.

Background

The claimed invention is directed to sustained release pharmaceutical comprising beraprost sodium (BPS). BPS is an active pharmaceutical ingredient having a high activity. As a result of this high activity, doses of BPS are small, resulting in a narrow therapeutic effect. Moreover, BPS's half life in blood can be as short as one hour. Therefore, to obtain the necessary therapeutic effect, the prior art suggests that BPS must be administered frequently.

BPS is an acidic API having a pH-dependent solubility in aqueous solutions. Thus, the release rate of BPS is largely influenced by pH, which changes along the gastrointestinal tract. As the pH changes, more or less BPS is released from the formulation. Potentially this could lead to high enough levels of BPS in the blood, which could produce unwanted side effects.

Moreover, merely admixing BPS in a sustained release matrix or merely coating BPS with a sustained release coating, results in pH-dependent release of the API, a release which is largely influenced by the pHs present in the gastrointestinal tract. The results are the same when formulating with an enteric coating since the enteric coating polymer, like the API, has pH-dependent solubility.

In view of this, Applicants developed a novel BPS formulation to provide a pH-independent, sustained release of BPS, which ultimately allows for a reduction in the number of administrations of BPS needed to maintain a therapeutic effect.

Hara in view of Samejima and Gowan

Hara does not disclose the pH-independent release of BPS or the use of the pH-independent polymers recited in claim 1. Instead, *Hara* is directed to an oral formulation comprising granules of a PGI_2-derivative which are coated with an enteric and/or water-insoluble material to provide sustained release granules. (*Hara*, page 4.) As examples of enteric coating materials, *Hara* recites various polymers including poly(methacrylic acid, methylmethacrylate) and poly(methacrylic acid, ethylacrylate). (*Id.* at 7.) *Hara* identifies these copolymers as "Euragit LS" having a solution pH in he range of pH 6-7 and "Eudragit L30D" having a solution pH of 5.5. (*Id.*) Each of these materials are pH-dependent polymers and are soluble in water having about a neutral pH. Thus, the use of these enteric materials, alone or in combination with other disclosed water-insoluble materials, provides for a pH-dependent release. Accordingly, *Hara* does not disclose the sustained release of BPS in a pH-independent manner as in the claimed invention or the use of the claimed pH-independent polymers recited in claim 1.

Moreover, Hara does not disclose the use of a second skin layer or the importance of an additional layer to effect pH-independent release. This is particularly important because Applicants have surprisingly shown that pH-independent sustained release cannot be attained by merely coating BPS with a monolayered water-insoluble sustained release film as in *Hara*. FIG. 3 of the present invention compares the pH-dependent release behavior, at pHs 1.2 and 6.8, between Formulation Example 18 (which represents a formulation of the claimed invention comprising two skin layers) and Comparative Example 2 (which represents the use of a mono-layer of a water-insoluble polymer, as in some embodiments of *Hara*). FIG. 3 clearly shows

that pH-dependent release behavior is improved by including a second skin layer as in the claimed invention. Indeed, the dissolution profiles for Formulation Example 18 tested at pH 1.2 and pH 6.8 are very similar, confirming that stable, pH-independent release was able to be obtained. (*Application*, page 12, lines 25-27.) This is in contrast to Comparative Example 2 where the release rates at pH 1.2 and 6.8 are quite different and hence show a pH-dependent release. (*Id.* at lines 21-24.) There is no disclosure in *Hara* to incorporate any of the claimed "skin layer" components or any material which would cause the PGI_2-derivative to be released in a pH-independent manner, let alone to include a second skin layer as in the claimed invention. In fact, Hara provides no mention of pH-independent release at all and certainly no disclosure that such a property is even desirable. Consequently, one skilled in the art would not look to *Hara* for any guidance to make the sustained-release BPS formulation of the claimed invention.

Neither *Samejima* or *Gowan* cure the deficiencies of *Hara*. *Samejima* is directed to a controlled release pharmaceutical preparation comprising a core containing an API and a porous film coating comprising either (1) a hydrophobic polymeric substance, or (2) a combination of a hydrophobic polymeric substance and a hydrophilic polymeric substance. (*Samejima*, abstract.) *Samejima* discloses many examples of different hydrophobic and hydrophillic polymers which could be utilized to provide films having varying porosities and hence, different API release rates. (*Id.* at col.2 to col.13; col.6 ll.37-45.) In this regard, *Samejima* discloses the application of polymer films to control API release much like in Comparative Example 2 of the claimed invention. And, as already detailed above, such porous film coatings cannot offer a sustained release of an API having a pH-dependent solubility. Moreover, *Samejima* provides no disclosure to pick and choose any specific combination of

polymers to ensure a pH-independent release, let alone to select any of the "skin layer" components of the claimed invention. Nor does it disclose a second skin layer as in the claimed invention. Therefore, even if the teachings of *Samejima* were combined with *Hara*, the combination would not result in the claimed invention.

Gowan is directed to a technique for taste masking granules by coating them with a hot-melt base material. (*Gowan*, col.1 ll.7-12.) *Gowan* does not disclose that any of the "hot-melt base materials" can be selected to alter the drug release profile of a formulation, let alone to provide a sustained release of BPS as in the claimed invention. Nor is there any disclosure that adding a taste-masking "hot-melt base material" could allow for pH-independent release of an API having a pH-dependent solubility. Accordingly, even if the collective teachings of *Hara*, *Samejima*, and *Gowan* were combined, the combination would not result in the claimed invention. Moreover, even after *KSR v. Teleflex*, 550 U.S. 398, 402 (2007), it is not enough that certain elements could be combined. There must be some reason to suppose that they would be combined and nothing in the collective teachings of the cited art leads to the conclusion that the films of *Samejima* or materials of *Gowen* would be combined with the formulation of *Hara* to provide for a sustained release of BPS as in the claimed invention. Therefore, the rejection should be withdrawn. *See* also *United States v. Adams*, 383 U.S. 39, 50-52 (1965).

Hara in view of Liversidge and Kokubo

Applicants submit that that even if *Hara*, *Liversidge*, and *Kokubo* were combined, the collective teachings would not result in the claimed invention. As already recited above, *Hara* does not teach the use of the claimed pH-independent polymer derivatives or the sustained release of BPS in a pH-independent manner. Neither *Liversidge* nor *Kokubo* cure this deficiency.

Liversidge is directed to stable, dispersible drug nanoparticles and a method for preparing such particles by wet milling. (*Liversidge*, col.3 ll.16-31.) The reference as a whole does not disclose the modification of a formulation to provide a sustained release of an API. Indeed, there is no disclosure in *Liversidge* that modifying particle size would result in the sustained release of BPS as in the claimed invention. Nor is there any disclosure in *Liversidge* of combining any pH-independent polymers with BPS to provide sustained release as in the claimed invention.

Kukobo is directed to a masking technique where a "hot-melt base material" is coated on granules. (*Kukobo*, Abstract.) *Kukobo* does not disclose that any of these "hot-melt base materials" can be selected to alter the drug release profile of a formulation, let alone to provide a sustained release of an API. Nor is there any disclosure that adding a "hot-melt base material" would allow for pH-independent release of an API having a pH-dependent solubility. Accordingly, even if the collective teachings of *Hara*, *Liversidge*, and *Kukobo* were combined, the combination would not result in the claimed invention and, thus the rejection should be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

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